REMARKS

Amendments in the claims

Following entry of the present amendment, Claims 12–31 are pending in the present application, of which Claims 20–28 are presently withdrawn from consideration. Claims 1–11 were previously canceled. Claims 29–31 are added by the present amendment.

Claims 12, 13 and 17 are amended to further enhance clarity by minor rewording (*e.g.*, insertion of "administration" in place of "administering"; and rendering of "solvent", "crystallization inhibitor" and "dispersant" in singular in place of plural form).

New Claims 29–31 are drawn to embodiments of the invention wherein a transdermal system contains rotigotine base in an amount permitting a flow rate of rotigotine through human skin that is therapeutically effective, upon application of the system at intervals of 1 to 7 days, for treatment of morbus Parkinson (Claim 29), restless leg syndrome (Claim 30) or depression (Claim 31). Support for these claims is found in the specification as filed, as follows:

- therapeutically effective flow rate through human skin – at least at p. 3, second paragraph and p. 5, second paragraph;
- application intervals of 1 to 7 days – at least at the paragraph bridging pp. 11–12;
- treatment of morbus Parkinson, restless leg syndrome and depression – at least at p. 13, fourth paragraph.

New Claims 29–31 depend from Claim 17 and accordingly fall within the presently elected invention.

No new matter is introduced as a result of the present amendment.

RESPONSE TO OFFICE ACTION DATED 6 MARCH 2009

1. Priority

The present Action makes no comment on Applicant's response that an English-language translation of the foreign priority application is not required at this time. Applicant believes, therefore, that this matter is settled.

2. Drawings

Figs. 1–6 are objected to as being of poor quality. Applicant attaches replacement copies of Figs. 1–6 that are believed to meet Office requirements, in accordance with 37 C.F.R. §1.84 and §1.121(d). These replacement drawings incorporate no substantive amendment and no new matter is introduced thereby.

3. Rejection under 35 U.S.C. §103(a)

Claims 12–19 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent Application Publication No. 2003/0027793 ("Lauterbach", misspelled "Lauterback" on that publication) in view of U.S. Patent No. 5,906,830 ("Farinas") and International Patent Publication No. WO 92/014442 ("Taylor"). This rejection is respectfully traversed.

At the outset, Applicant maintains that Lauterbach does not constitute statutory prior art under 35 U.S.C. §102(b), and no admission is made herein that the disclosure of Lauterbach constitutes prior art to the present invention under any section of 35 U.S.C. §102. The publication date of Lauterbach (6 February 2003), is later than the earliest priority date of the present application (30 December 2002). The Examiner's attention is respectfully drawn to International Patent Publication No. WO 02/089777, published 14 November 2002, which appears to be a counterpart of the Lauterbach reference. Applicant reserves the right to make a showing of earlier invention to disqualify Lauterbach. However, such a showing is unnecessary, as even if Lauterbach represented prior art to the present invention, Lauterbach would not render the present claims obvious, for reasons set forth below.

Applicant has stated that a significant distinction between the instant claims and the Lauterbach art lies in the fact that the matrix of the present invention is free of solvents, crystallization inhibitors and dispersants. In maintaining this rejection, the Examiner, first, re-

asserts the combination of Lauterbach and Farinas, stating: "Because Lauterbach lacks this teaching [a matrix free of solvents, crystallization inhibitors and dispersants], the examiner combined Lauterback with Farinas" (Action, p. 8, lines 13–14). Second, in making the present three-way combination, the Examiner states: "Taylor is only incorporated for the teaching of its particle sizes regardless if they are crystal particles" (Action, passage bridging pp. 11–12). The Examiner's proffered rationale for combining the three documents is that "[o]ne would have been motivated to do so in order to obtain higher drug fluxes and a controlled release rate, as suggested by Farinas and Taylor respectively (Action, p. 12, lines 7–9; see also p. 9, last two lines).

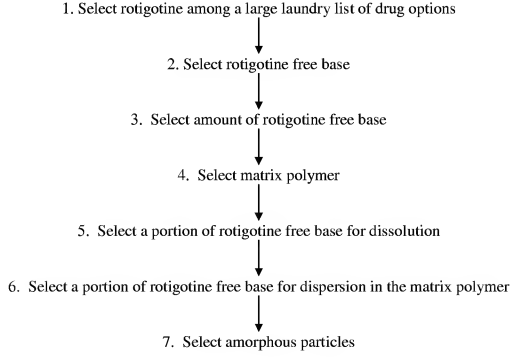
In making a combination/modification rejection such as this, the prior art must be considered in its entirety, including disclosures that teach away from the claims. MPEP 2141.03. As discussed previously, Lauterbach (the only cited reference to discuss the specific drug rotigotine) and WO 99/49852 teach use of additives to improve the solubility of rotigotine in a matrix. Specifically, as discussed in the present specification as filed at p. 2, lines 18–20: "Rotigotine is only feebly soluble in hydrophobic polymers such as silicon[e], for example. For these reasons, in WO 99/49852 the adding of additives to improve the solution characteristics of the rotigotine is recommended." Lauterbach references WO 99/49852, for example at paragraphs **[0011]–[0013]** thereof, and in the preparation example thereof includes such an additive, namely polyvinylpyrrolidone (PVP), together with rotigotine base in a silicone matrix (Lauterbach, paragraphs **[0037]–[0041]**). Therefore, as discussed previously, the art of record emphasizes the importance of using a solubility-enhancing ingredient such as PVP in providing a silicone polymer/rotigotine base matrix providing acceptable skin flux of rotigotine.

With this background, one of ordinary skill in the art when reading Farinas and Taylor together with Lauterbach would not be motivated to modify Lauterbach to arrive at the presently claimed invention.

First, an ordinarily skilled artisan reading Farinas would be more than likely to include crystallization inhibitors, *etc.* because of the express teaching of Lauterbach and WO 99/49852 cited therein. The Action interprets Farinas's statement that "[t]he drug formulation may also include standard carriers or vehicles useful for facilitating drug delivery" (emphasis added) as

a suggestion of possible exclusion of crystallization inhibitors. Applicant respectfully disagrees with this interpretation. Farinas recites an advantage of inclusion (facilitation of drug delivery) but not of exclusion, therefore on balance the motivation in Farinas to one of ordinary skill in the art is to include a crystallization inhibitor. However, even if Farinas were read to be neutral on the question of inclusion or exclusion, exclusion of crystallization inhibitors specifically with rotigotine (not mentioned in Farinas) would nonetheless be contrary to accepted wisdom in the art, as evidenced by Lauterbach and WO 99/49854. Applicant's move away from accepted wisdom in the art is evidence of nonobviousness. MPEP 2145 X.D.3.

Second, Farinas contains no elaboration or pattern of preferences that point the ordinarily skilled artisan away from its generic disclosure toward Applicant's invention. Such an artisan reading Farinas would need to take a sequence of at least nine steps to arrive at the presently claimed invention. Below is a flow chart of exemplary selections (not exhaustive) that the artisan would have to make in order to obtain a transdermal therapeutic system (TTS) having rotigotine characterized by being partly dissolved in a matrix and partly in the form of amorphous particles dispersed in the matrix, the amorphous particles having a maximum mean diameter of 30 μm:



8. Select maximum mean diameter size

9. Select absence of solvent, crystallization inhibitor and dispersant

Clearly, impermissible hindsight would have to be used to conclude that one of ordinary skill in the art would make all of these selections, amongst others, and then apply these selections to modify Lauterbach, especially when Lauterbach expressly teaches that the specific drug rotigotine should be used with a solubility-enhancing ingredient such as PVP. Only from reading Applicant's specification would one learn, contrary to accepted wisdom, that rotigotine can be used satisfactorily without crystallization inhibitors, *etc.*

At best, the very large number of possible selections in Farinas provide a possible invitation to "try" or "experiment". But Farinas, alone or in combination with Lauterbach, provides neither guidance nor suggestion to arrive at the claimed invention. Additionally, although both Farinas and the present invention employ 'melting' to obtain the specific TTS, simple extrapolation from estradiol (a steroid) to rotigotine is unlikely to work. Thus, in this instance, what might have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices in the hope of eventually arriving at a successful result. Thus, the invention as defined in Claims 12 and 13 can not be obvious over Lauterbach and Farinas.

Further, the Action (p. 8, lines 19–20) states: "Farinas teaches heating an admixture of polymer and rotigotine to a temperature that is higher than the actual melting temperature of the pure drug contained in the formulation…". On the contrary, no such teaching relating to rotigotine, in particular rotigotine free base, is found in Farinas. Moreover, there is no mention of rotigotine anywhere in Farinas. Additionally, although Farinas reports "heating a particular polymer-admixture" at col. 6, rotigotine is sensitive to oxidation and therefore heating rotigotine must be performed very carefully.

Regarding Taylor, the Action (p. 11, lines 8–10) admits that Taylor was "solely cited to disclose the particle size in the instant claims and to establish the state of the prior art." To avoid a 'piecemeal' approach to claim examination, a claim must be considered as a whole

and viewed against the entirety of the pertinent prior art. Taylor is not pertinent and has no relevance to the present invention, therefore one would not look to Taylor to combine it with Lauterbach and Farinas. For example, Taylor

(1) does not mention rotigotine or dopamine agonists,

(2) does not use a matrix polymer,

(3) does not teach amorphous particles, and

(4) uses propylene glycol or glycerol in examples thereof to produce a 'paste'.

More importantly, it is well known that particle size depends on, amongst other factors, (1) the drug employed, (2) the formulation employed and (3) the manufacturing process. Therefore, reliance on Taylor solely for disclosure of solid crystals, not even amorphous particles, predominantly sized less than 20 μm, has no bearing on the presently claimed invention and provides no guidance toward modification of the proposed Lauterbach and Farinas combination.

Next, the Action (p. 9, lines 17–21) asserts that "[b]ecause Farinas teaches that dopaminergic agonists can be used as active agents in its supersaturated drug reservoirs, one would have predicted with a reasonable expectation of success that the rotigotine transdermal delivery system of Lauterbach could be modified to include characteristics of Farinas, including its elimination of solvents, crystallization inhibitors and dispersants."

First, as stated above, Farinas is too generic and teaches too many possible systems to lead to expectation that all such systems would be successful, or indeed that any one system would have reasonable expectation of success. It is plainly incredible that an ordinary artisan could predict with any reasonable expectation of success that specifically rotigotine could work without solvent, crystallization inhibitor and dispersant, and further that specifically rotigotine could work in any one of the numerous possible systems of Farinas, just because Farinas mentions dopaminergic agonists as one of many possible classes of active agents that may be used. Since Lauterbach is the only reference cited which specifically mentions rotigotine, Lauterbach should be afforded more weight than Farinas's generic disclosure, therefore one of ordinary skill in the art would have expected to need a crystallization inhibitor, *etc.* for success. It is well known that the performance of active agents obviously

depends significantly on the character of the active agent, formulation conditions and manufacturing conditions.

Second, the Office has yet to appreciate that even if *arguendo* one of ordinary skill would somehow have been motivated to: (1) remove the crystallization inhibitors taught in Lauterbach and WO 99/49852 and (2) prepare a matrix comprising rotigotine free base amorphous particles with (3) a maximum mean diameter of 30 µm, that it could not have been predicted that after 12 months storage, no signs of rotigotine crystallization or change in particle size would be observed, as disclosed in the present specification as filed at p. 6, lines 4–5.

Therefore, Applicant maintains that with respect to Claim 12, it could not have been predicted by one of skill in the art at the time of the present invention that a storage-stable matrix could be prepared containing rotigotine base above its limit of solubility in the matrix polymer, yet without solvents, crystallization inhibitors or dispersants. With respect to Claim 13, it could not have been predicted by one of skill in the art at the time of the present invention that a storage-stable matrix could be prepared containing rotigotine base above its limit of solubility in the matrix polymer, yet without any excipient ingredient other than the matrix polymer and, optionally, one or more antioxidants. The Office has offered no evidence or rationale as to how one of ordinary skill in the art could have predicted that the claimed TTS formulation of rotigotine could achieve these results.

Therefore, Applicant submits that no *prima facie* case of obviousness has been established, at least for the following reasons.

- Lauterbach expressly teaches use of rotigotine with crystallization inhibitors, *etc.*
- The generic disclosure of Farinas does not provide any motivation to modify Lauterbach in the direction of Applicant's claims.
- Taylor is not relevant to the proposed Lauterbach and Farinas combination.
- No reasonable expectation of success existed that a TTS containing a matrix polymer wherein rotigotine is partly dissolved and partly present as amorphous particles having a maximum mean diameter of 30 um, and wherein the matrix is free of solvent, crystallization inhibitor and dispersant, would work.

- In particular, no expectation of success can reasonably be postulated as to achieving a storage-stable polymer matrix containing amorphous particles of rotigotine free base.

The Office has thus failed to make a case of *prima facie* obviousness with respect to Claims 12 and 13. Each of Claims 14–19 depends directly or ultimately from Claim 12 or 13 and incorporates all limitations of Claim 12 or 13, and is therefore nonobvious for at least the same reasons that Claims 12 and 13 are nonobvious. Withdrawal of the present rejection is respectfully requested.

3. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated or rendered moot herein. Applicant therefore respectfully requests that all presently outstanding rejections be re-considered and withdrawn. It is believed that a full and complete response has been made to the present Action and that the application is in condition for allowance.

Should any issues remain, the Examiner is invited to call the undersigned at the telephone number given below.

Respectfully submitted,

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Attachment:
Replacement drawings (Sheets 1–6 of 6)